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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,677	10/17/2003	John Guy	5853-324	9515

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Stanley A. Kim, Ph.D., Esq.
Akerman Senterfitt
Suite 400
222 Lakeview Avenue
West Palm Beach, FL 33402-3188

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
06/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/687,677	GUY, JOHN	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-25* is/are pending in the application.

4a) Of the above claim(s) *19-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 3/19/07 has been entered. Claim 2 was cancelled. Claims 1, and 3-25 are pending. Claims 1, and 3-15 were amended.

Claims 19-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

This application 10/687,677 filed on October 17, 2003 claims the benefit of 60/419,435 filed on 10/18/2002.

Status of claims: Claims 1, and 3-18 are currently under examination.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. The rejection of claims 1, and 3-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, are ***withdrawn*** because the combination of claim amendments and Applicant's arguments are found persuasive.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 1, 3-18 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are ***withdrawn*** because claim 1, and 3-15 have been amended.

Claims 1 and 3-15 have been amended and no longer recite " a *non-naturally occurring* nucleic acid". Claims 16-18 depend from claim 15.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1, and 8-16 as amended remain rejected under 35 U.S.C. 102(b) as being anticipated by Guy (Guy, Gene therapy for nuclear complementation of the G11778A LHON mitochondrial DNA mutation, Neurology, (April 24, 2001) Vol. 56, No. 8 Supplement 3, pp. A14. print. Meeting Info.: 53rd Annual Meeting of the American Academy of Neurology. Philadelphia, PA, USA. May 05-11, 2001. American Academy of Neurology. CODEN:

NEURAI. ISSN: 0028-3878). Previous rejection is ***maintained*** for the reasons of record advanced on pages 7-8 of the office action mailed on 12/18/06.

Applicant's Arguments

Applicant argues that Guy 2001 neither teaches nor discloses the mutations required for a functional ND4 protein. The disclosure by Guy is non-enabling and as such one of ordinary skill in the art could not construct the instant invention based on Guy 2001. Furthermore, Guy 2001 fails to teach an isolated nucleic acid comprising the ND4 gene. As such Guy fails to teach each and every claim limitation.

Response to Applicant's Arguments

It is noted that for art rejection, the key determinant is whether the art disclosed the limitations of claimed invention for instant application. Specifically, for rejection under 35 USC 112 first paragraph, as stated in the preceding section, the claimed language reads on any sequence variants of ND4, which is deemed not enabled in light of lack of functional assay in the specification of instant application for an skilled artisan to determine if any given variant is functional. However, the recited 102 (b) prior art by Guy is, in fact, applicant's own publication in a scientific meeting, which is presumed enabled unless Guy (the inventor of instant application) declares otherwise on the record. In this regard, Guy disclosed the successful import of ND4flag fusion protein into 5-10% of the transfected G11178 cybrid cell and the rate of ATP synthesis in the transfected G11778A cybrids was reduced 63% relative to the control cell line.

More elaboration of the teachings by Guy 2001 is documented below. Guy 2001 disclosed that, "the feasibility of complementing a mutation in the mitochondrial subunit ND4

(G1178A) was tested by *construction* of a nuclear encoded version of wild-type ND4. Codon read in a non-canonical fashion by the mitochondrial genetic system, such as the UGA codon that directs the insertion of tryptophan in mitochondria, but is a stop codon in the cytoplasm were converted to the universal genetic codon" (See Design/Method Guy et al., 2001). It is noted that "*construction* of a nuclear encoded version of wild-type ND4" clearly reads on *isolated* nucleic acid encoding a functional ND4 as recited in claim 1, whereas the statement "Codons read in a non-canonical fashion by the mitochondrial genetic system, such as the UGA codon that directs the insertion of tryptophan in mitochondria, but is a stop codon in the cytoplasm were converted to the universal genetic codon" clearly reads on claim 7 of instant application.

With regard to the enhancer element (claim 13 of instant applicant), the recombinant Adeno-associated virus (AAV) vector taught by Guy reads on the CMV enhancer element because the CMV enhancer element is common composition of an AAV vector. This is evident and supported by Guy et al., Rescue of a mitochondrial deficiency causing Leber Hereditary Optic Neuropathy. *Ann Neurol.* 52(5): 534-42, 2002, published online October 11, 2002.

Thus Guy clearly anticipates amended claims 1, 2, and 8-16 of instant application.

4. Claims 1, 3-6, and 8-18 as amended remained rejected under 35 U.S.C. 102(a) as being anticipated by Guy et al. (Guy et al., Rescue of a mitochondrial deficiency causing Leber Hereditary Optic Neuropathy. *Ann Neurol.* 52(5): 534-42, 2002, published online *October 11, 2002*). Previous rejection is ***maintained*** for the reasons of record advanced on pages 9-10 of the office action mailed on 12/18/06.

Applicant's Arguments

Applicant argues that Guy et al., 2002 do not teach or disclose an isolated nucleic acid, which encodes a functional ND4 protein. Applicant also argues that Guy et al. 2002 discuss a mutation, however, Guy et al., 2002 do not teach or disclose the mutations that are required as taught by Applicants. Guy et al. is a non-enabling reference for the instant invention. For example, Guy et al., 2002 refers to one mutation out of any possible number of substitutions such as those taught by Applicants. Furthermore, Applicants note that the instant application claims priority to U.S.S.N. 60/419,435 filed October 18, 2002. The cited referenced was published online, according to the Examiner, October 11, 2002. Applicants further stated that if the Examiner would prefer, Applicants could file a 37 C.F.R. § 1.131 declaration to antedate their findings and show that Applicants conceived and reduced to practice the instant invention prior to the publication date of the cited reference.

Response to Applicant's Arguments

Guy et al., 2002 is also applicant's own publication, which was published 7 days before the claimed priority date of instant application. Guy et al. 2002 teach that a G to A transition at nucleotide 11778 in the ND4 subunit gene of complex I was the first point mutation in the mitochondrial genome linked to a human disease. It causes Leber Hereditary Optic Neuropathy, a disorder with oxidative phosphorylation deficiency. To overcome this defect, Gut et al. 2002 made a synthetic ND4 subunit compatible with the "universal" genetic code and imported it into mitochondria by adding a mitochondrial targeting sequence (which clearly reads on isolated nucleic acid comprising a nucleic acid sequence encoding a functional ND4 mitochondrial protein as recited in claimed invention of instant application). For detection, Guy et al. added a

FLAG tag. This gene was inserted in an adeno-associated viral vector. The ND4FLAG protein was imported into the mitochondria of cybrids harboring the G11778A mutation, where it increased their survival rate threefold, under restrictive conditions that forced the cells to rely predominantly on oxidative phosphorylation to produce ATP. More elaboration on the teachings of Guy et al. 2002 has been documented on pages 9-10 in the Non-Final rejection.

Thus Guy et al. clearly anticipates claims 1, 3-6, and 8-18 as amended of instant application.

To overcome this 102(a), the Examiner agrees with Applicants that Applicants can file a 37 C.F.R. § 1.131 declaration to antedate their findings and show that Applicants conceived and reduced to practice the instant invention prior to the publication date of the cited reference. However, such a submission after final is cause for non-entry of any amendment filed after prosecution has closed.

5. Claims 1, 8, 10-12, 15-18 as amended remain rejected under 35 U.S.C. 102(a) as being anticipated by Guy et al. (Guy et al., Gene therapy with the ND4 subunit gene recoded in the universal genetic code reverses a mitochondrial deficiency causing Leber Hereditary Optic Neuropathy (LHON), Neurology, (April 9, 2002) Vol. 58, No. 7 Supplement 3, pp. A508. print. Meeting Info.: 54th Annual Meeting of the American Academy of Neurology. Denver, Colorado, USA. April 13-20, 2002. CODEN: NEURAI. ISSN: 0028-3878). Previous rejection is ***maintained*** for the reasons of record advanced on pages 10-11 of the office action mailed on 12/18/06.

Applicant's Arguments

Applicants argue that Guy et al, 2002 discuss a fusion protein of ND4. The instant invention is directed to a an isolated nucleic acid comprising a nucleotide sequence encoding a functional ND4 mitochondrial protein wherein said sequence comprises at least one codon substitution of a mitochondrial codon with a nuclear codon. Applicants further argue that Guy et al., 2002 do not teach or disclose an isolated nucleic acid encoding a functional ND4 mitochondrial protein. Furthermore, Applicants stated that Applicants could submit a declaration to show that the date of conception of the instant invention is prior to the publication date indicated in the office action.

Response to Applicant's Arguments

Guy et al., 2002 is also applicant's own publication, which was published more than six months before the claimed priority date of instant application. Guy et al. 2002 teach construction of recoded ND4 with FLAG tag which clearly reads on isolated nucleic acid comprising a nucleic acid sequence encoding a functional ND4 mitochondrial protein as recited in claimed invention of instant application. More elaboration on the teachings of Guy et al. 2002 has been documented on pages 10-11 in the Non-Final rejection.

Thus Guy et al. clearly anticipates claims 1, 8, 10-12, 15-18 as amended as amended of instant application.

To overcome this 102(a), Examiner agrees with Applicants that Applicants can file a 37 C.F.R. § 1.131 declaration to antedate their findings and show that Applicants conceived and reduced to practice the instant invention prior to the publication date of the cited reference.

However, such a submission after final is cause for non-entry of any amendment filed after prosecution has closed.

6. Claims 1, 3-6, and 8-18 as amended remain rejected under 35 U.S.C. 102(e) as being anticipated by Manfredi et al. (Manfredi et al., U.S. Patent Application Publication No: 2004/0072774, Publication date, April15, 2004, which claims benefits of provisional application No. 60/358,935, filed on Feb. 23, 2002). Previous rejection is ***maintained*** for the reasons of record advanced on pages 12-14 of the office action mailed on 12/18/06.

Applicant's Arguments

Applicants argue that Applicants invention is directed in part to an isolated nucleic acid comprising a nucleotide sequence encoding a functional ND4 mitochondrial protein wherein the sequence comprises at least one codon substitution of a mitochondrial codon with a nuclear codon. Applicants also teach a cell comprising the isolated nucleic acid. Manfredi discusses the introduction of a peptide into an organelle, more specifically an ATPase 6. Manfredi does not teach or disclose the instant invention. Furthermore, Manfredi does not teach or disclose each and every claim limitation of the instant invention.

Response to Applicant's Arguments

Manfredi et al. teach methods for introducing functional peptides into organelles. Additionally, the present invention provides a method for correcting a phenotypic deficiency in a mammal that results from a mutation in the mammal's mitochondrial DNA (mtDNA). The invention by Manfredi et al. further provides a method for treating a mitochondrial disorder in a subject in need of treatment therefor. Also provided is an expression vector that is useful for

introducing a functional peptide encoded by an mtDNA sequence into a mitochondrion. The invention by Manfredi et al. also provides eukaryotic cells transformed by expression vectors that are useful for introducing functional peptides into organelles. Finally, the invention by Manfredi et al. provides a pharmaceutical composition comprising a non-nuclear nucleic acid sequence encoding a peptide for introduction into an organelle, a nucleic acid sequence encoding an organelle-targeting signal, and a pharmaceutically acceptable carrier (See abstract, Manfredi et al.).

With regard to a non-naturally occurring nucleic acid (claim 1 of instant application), Manfredi et al. teach an expression vector that is useful for introducing a functional peptide encoded by a mitochondrial DNA (mtDNA) sequence into a mitochondrion, comprising: (a) a nucleic acid sequence encoding ATPase 6 subunit of F_0F_1-ATP synthase or *ND4* subunit of complex I, wherein the nucleic acid sequence is compatible with the *universal genetic code*; and (b) a nucleic acid sequence encoding a mitochondrial-targeting signal, wherein the mitochondrial-targeting signal is selected from the group consisting of the N-terminal region of human cytochrome c oxidase subunit VIII, the N-terminal region of the P1 isoform of subunit c of human ATP synthase, and the N-terminal region of the aldehyde dehydrogenase targeting sequence (See claim 75, Manfredi et al.). More elaboration on the teachings of Manfredi et al. has been documented on pages 12-14 in the Non-Final rejection.

Thus Manfredi et al. clearly anticipates claims 1, 3-6, and 8-18 as amended of instant application.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Valbertoglio
AU1632

Wu-Cheng Winston Shen, Ph. D.
Patent Examiner
Art Unit 1632